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(56) Documents Cited

EP 0600834 A1 WO 95/30421 A1 WO 95/28145 A1
US 5488041 A US 4980171 A

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(54) Abstract Title

Bisphosphonate Dosing Regimen

(57) A continuous dosing regimen for the treatment of conditions such as osteoporosis, Paget's disease, bone fracture, periodontal disease or hypercalcaemia comprises the administration of bisphosphonates, preferably alendronate, in relatively high unit dosages at intervals selected from the group consisting of once-weekly, twice-weekly, biweekly or twice-monthly dosing. The dosage regimen is effective in minimising adverse gastrointestinal problems such as oesophagitis and dyspepsia.

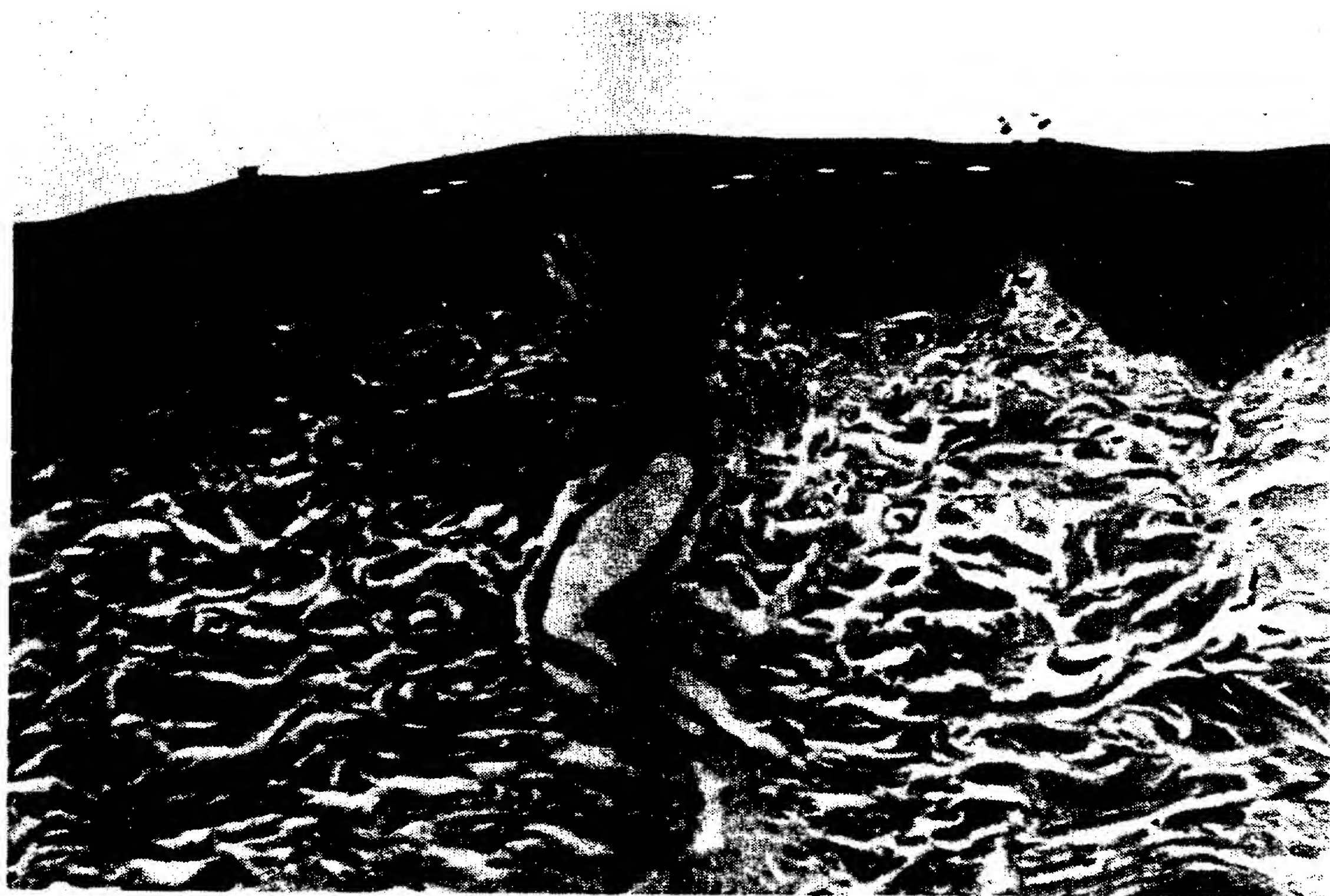


FIG. 1



FIG.2

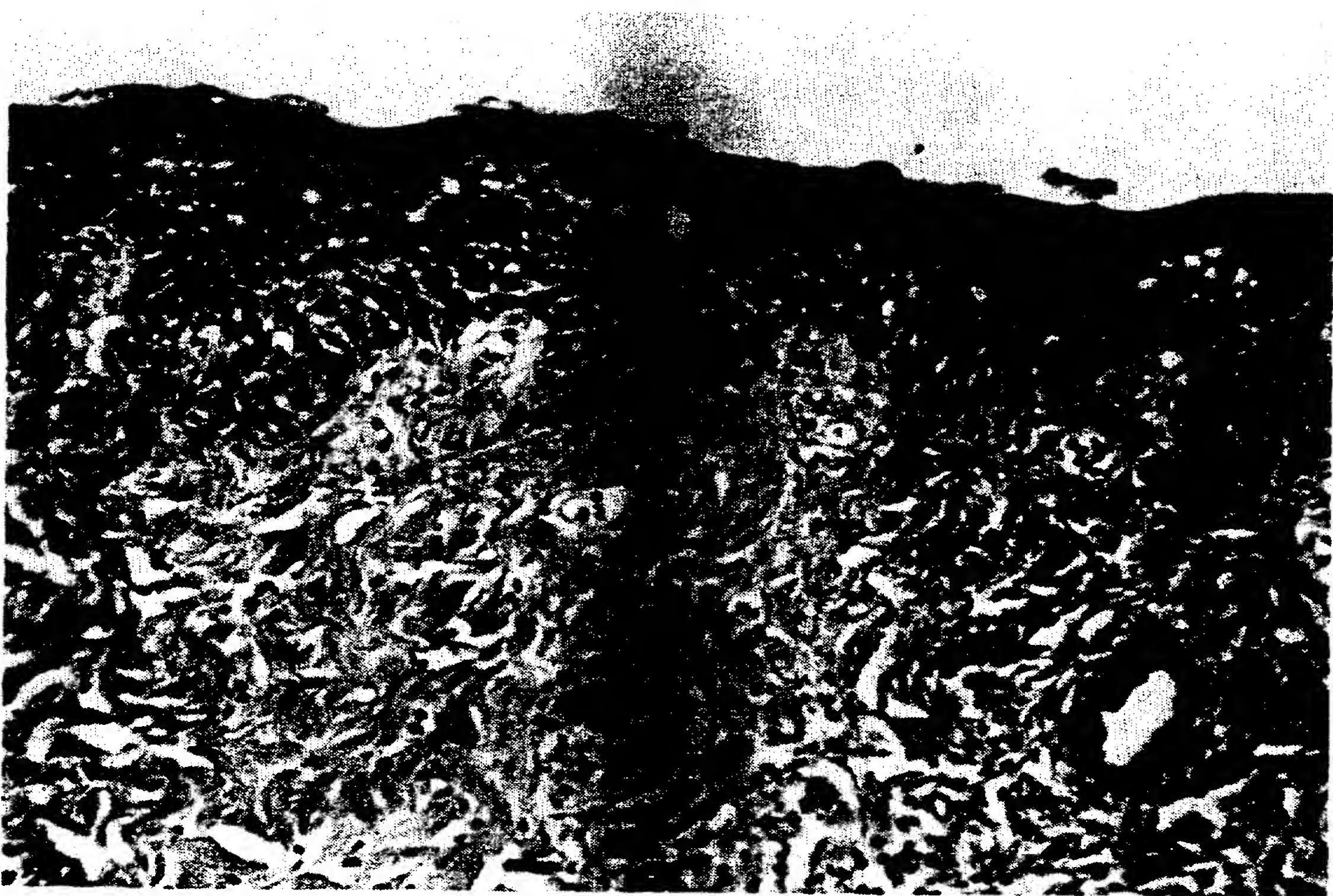


FIG.3



FIG.4

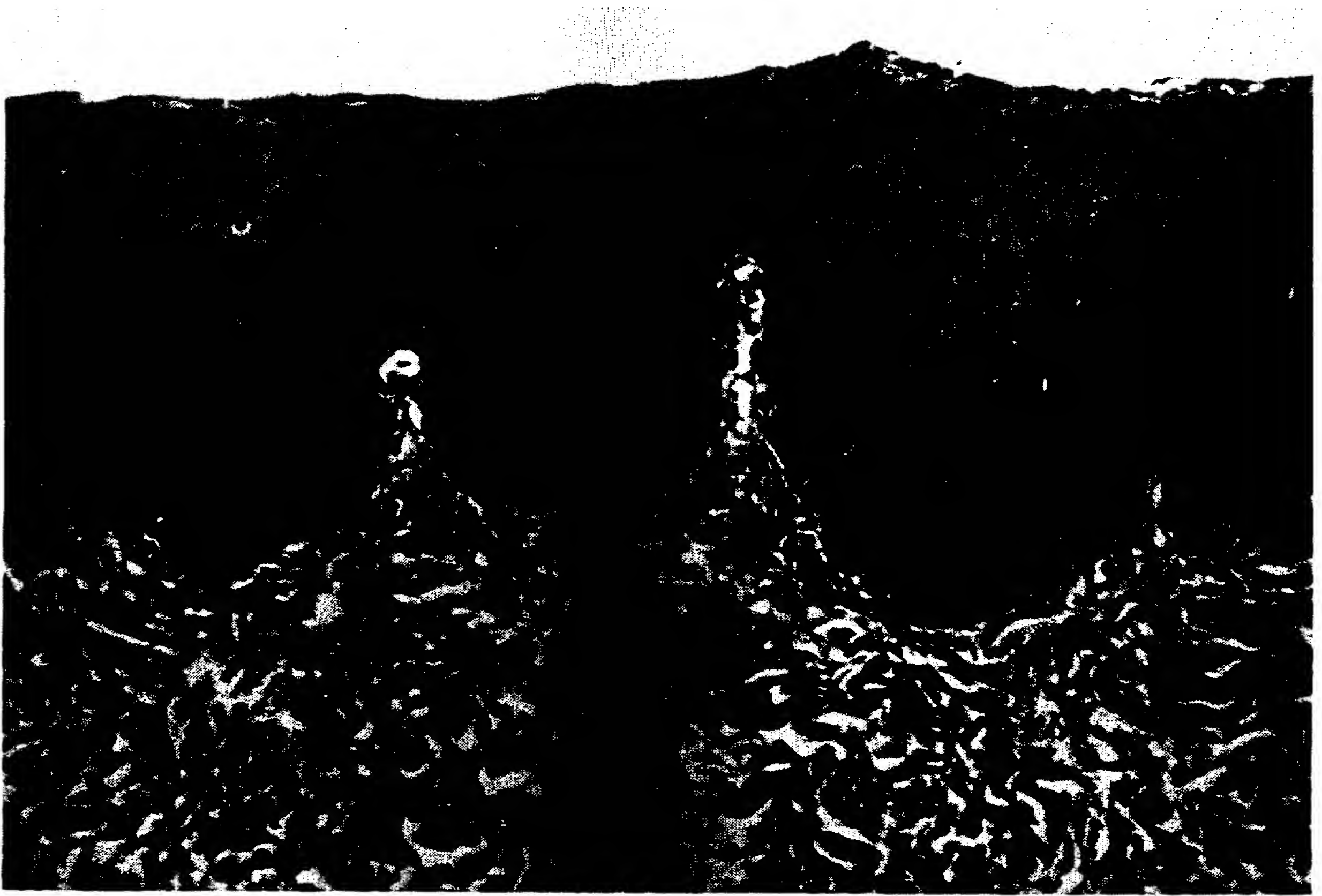


FIG.5



FIG.6



FIG.7



FIG.8

TITLE OF THE INVENTION
METHOD FOR INHIBITING BONE RESORPTION

CROSS-REFERENCE TO RELATED APPLICATIONS

5 This application is a continuation-in-part of
PCT/US98/14796, filed July 17, 1998, and also claims priority to U.S.
provisional applications Serial Nos. 60/053,535, filed July 23, 1997, and
60/053,351, filed July 22, 1997, both now abandoned, the contents of all of
the foregoing of which are hereby incorporated by reference in their
10 entirety.

FIELD OF THE INVENTION

 The present invention relates to oral methods for inhibiting
bone resorption in a mammal while minimizing the occurrence of or
15 potential for adverse gastrointestinal effects. These methods comprise
orally administering to a mammal in need thereof of a pharmaceutically
effective amount of a bisphosphonate as a unit dosage according to a
continuous schedule having a dosing interval selected from the group
consisting of once-weekly dosing, twice-weekly dosing, biweekly dosing,
20 and twice-monthly dosing. The present invention also relates to
pharmaceutical compositions and kits useful for carrying out these
methods.

BACKGROUND OF THE INVENTION

25 A variety of disorders in humans and other mammals
involve or are associated with abnormal bone resorption. Such disorders
include, but are not limited to, osteoporosis, Paget's disease,
periprosthetic bone loss or osteolysis, metastatic bone disease,
hypercalcemia of malignancy, multiple myeloma, periodontal disease,
30 and tooth loss. The most common of these disorders is osteoporosis,
which in its most frequent manifestation occurs in postmenopausal
women. Osteoporosis is a systemic skeletal disease characterized by a
low bone mass and microarchitectural deterioration of bone tissue, with
a consequent increase in bone fragility and susceptibility to fracture.
35 Because osteoporosis, as well as other disorders associated with bone

loss, are chronic conditions, it is believed that appropriate therapy will generally require chronic treatment.

5 Multinucleated cells called osteoclasts are responsible for causing bone loss through a process known as bone resorption. It is well known that bisphosphonates are selective inhibitors of osteoclastic bone resorption, making these compounds important therapeutic agents in the treatment or prevention of a variety of generalized or localized bone disorders caused by or associated with abnormal bone resorption. See H. Fleisch, *Bisphosphonates In Bone Disease, From The Laboratory*
10 *To The Patient*, 2nd Edition, Parthenon Publishing (1995), which is incorporated by reference herein in its entirety.

At present, a great amount of preclinical and clinical data exists for the potent bisphosphonate compound alendronate. Evidence suggests that other bisphosphonates such as risedronate, tiludronate,
15 ibandronate and zolendronate, have many properties in common with alendronate, including high potency as inhibitors of osteoclastic bone resorption. An older bisphosphonate compound, etidronate, also inhibits bone resorption. However, unlike the more potent bisphosphonates, etidronate impairs mineralization at doses used clinically, and may give
20 rise to osteomalacia, a condition resulting in an undesirable decrease in bone mineralization. See Boyce, B. F., Fogelman, I., Ralston, S. et al. (1984) *Lancet* 1(8381), pp. 821-824 (1984), and Gibbs, C. J., Aaron, J. E.; Peacock, M. (1986) *Br. Med. J.* 292, pp. 1227-1229 (1986), both of which are incorporated by reference herein in their entirety.

25 Despite their therapeutic benefits, bisphosphonates are poorly absorbed from the gastrointestinal tract. See B.J. Gertz et al., *Clinical Pharmacology of Alendronate Sodium, Osteoporosis Int.*, Suppl. 3: S13-16 (1993) and B.J. Gertz et al., *Studies of the oral bioavailability of alendronate, Clinical Pharmacology & Therapeutics*, vol. 58, number 3,
30 pp. 288-298 (September 1995), which are incorporated by reference herein in their entirety. Intravenous administration has been used to overcome this bioavailability problem. However, intravenous administration is costly and inconvenient, especially when the patient must be given an intravenous infusion lasting several hours on repeated occasions.

35 If oral administration of the bisphosphonate is desired,

relatively high doses must be administered to compensate for the low bioavailability from the gastrointestinal tract. To offset this low bioavailability, it is generally recommended that the patient take the bisphosphonate on an empty stomach and fast for at least 30 minutes afterwards. However, many patients find the need for such fasting on a daily basis to be inconvenient. Moreover, oral administration has been associated with adverse gastrointestinal effects, especially those relating to the esophagus. See Fleisch, Id. These effects appear to be related to the irritant potential of the bisphosphonate in the esophagus, a problem which is exacerbated by the presence of refluxed gastric acid. For example, the bisphosphonate, pamidronate has been associated with esophageal ulcers. See E.G. Lufkin et al., *Pamidronate: An Unrecognized Problem in Gastrointestinal Tolerability, Osteoporosis International*, 4: 320-322 (1994), which is incorporated by reference herein in its entirety. Although not as common, the use of alendronate has been associated with esophagitis and/or esophageal ulcers. See P.C. De Groen, et al., *Esophagitis Associated With The Use Of Alendronate, New England Journal of Medicine*, vol. 335, no. 124, pp. 1016-1021 (1996), D.O. Castell, *Pill Esophagitis -- The Case of Alendronate, New England Journal of Medicine*, vol. 335, no. 124, pp. 1058-1059 (1996), and U.A. Liberman et al., *Esophagitis and Alendronate, New England Journal of Medicine*, vol. 335, no. 124, pp. 1069-1070 (1996), which are incorporated by reference herein in their entirety. The degree of adverse gastrointestinal effects of bisphosphonates has been shown to increase with increasing dose. See C.H. Chestnut et al., *Alendronate Treatment of the Postmenopausal Osteoporotic Woman: Effect of Multiple Dosages on Bone Mass and Bone Remodeling, The American Journal of Medicine*, vol. 99, pp. 144-152, (August 1995), which is incorporated by reference herein in its entirety. Also, these adverse esophageal effects appear to be more prevalent in patients who do not take the bisphosphonate with an adequate amount of liquid or who lie down shortly after dosing, thereby increasing the chance for esophageal reflux.

Current oral bisphosphonate therapies generally fall into two categories: (1) those therapies utilizing continuous daily treatment,

and (2) those therapies utilizing a cyclic regimen of treatment and rest periods.

5 The continuous daily treatment regimens normally involve the chronic administration of relatively low doses of the bisphosphonate compound, with the objective of delivering the desired cumulative therapeutic dose over the course of the treatment period. However, continuous daily dosing has the potential disadvantage of causing adverse gastrointestinal effects due to the repetitive, continuous, and additive irritation to the gastrointestinal tract. Also, because
10 bisphosphonates should be taken on an empty stomach followed by fasting and maintenance of an upright posture for at least 30 minutes, many patients find daily dosing to be burdensome. These factors can therefore interfere with patient compliance, and in severe cases even require cessation of treatment.

15 Cyclic treatment regimens were developed because some bisphosphonates, such as etidronate, when given daily for more than several days, have the disadvantage of actually causing a decline in bone mineralization, i.e. osteomalacia. U.S. Patent No. 4,761,406, to Flora et al, issued August 2, 1988, which is incorporated by reference herein in
20 its entirety, describes a cyclic regimen developed in an attempt to minimize the decline in bone mineralization while still providing a therapeutic anti-resorptive effect. Generally, cyclic regimens are characterized as being intermittent, as opposed to continuous treatment regimens, and have both treatment periods during which the
25 bisphosphonate is administered and nontreatment periods to permit the systemic level of the bisphosphonate to return to baseline. However, the cyclic regimens, relative to continuous dosing, appear to result in a decreased therapeutic antiresorptive efficacy. Data on risedronate suggests that cyclic dosing is actually less effective than continuous
30 daily dosing for maximizing antiresorptive bone effects. See L. Mortensen, et al., *Prevention Of Early Postmenopausal Bone Loss By Risedronate*, *Journal of Bone and Mineral Research*, vol. 10, supp. 1, p. s140 (1995), which is incorporated by reference herein in its entirety. Furthermore, these cyclic regimens do not eliminate or minimize
35 adverse gastrointestinal effects, because such regimens typically utilize

periods of multiple daily dosing. Also, the cyclic regimens are cumbersome to administer and have the disadvantage of low patient compliance, and consequently compromised therapeutic efficacy. U.S. Patent No. 5,366,965, to Strein, issued November 22, 1994, which is
5 incorporated by reference herein in its entirety, attempts to address the problem of adverse gastrointestinal effects by administering a polyphosphonate compound, either orally, subcutaneously, or intravenously, according to an intermittent dosing schedule having both a bone resorption inhibition period and a no-treatment rest period.
10 However, the regimen has the disadvantage of not being continuous and regular, and requires nontreatment periods ranging from 20 to 120 days. PCT Application No. WO 95/30421, to Goodship et al, published November 16, 1995, which is incorporated by reference herein in its
15 entirety, discloses methods for preventing prosthetic loosening and migration using various bisphosphonate compounds. Administration of a once weekly partial dose of the bisphosphonate is disclosed. However, the reference specifically fails to address the issue of adverse gastrointestinal effects or to disclose administration of larger or multiple dosages.
20 It is seen from current teachings that both daily and cyclic treatment regimens have shortcomings, and that there is a need for development of a dosing regimen to overcome these shortcomings.
In the present invention, it is found that the adverse gastrointestinal effects that can be associated with daily or cyclic dosing
25 regimens can be minimized by administering the bisphosphonate at a relatively high unit dosage according to a continuous schedule having a dosing interval selected from the group consisting of once-weekly dosing, twice-weekly dosing, biweekly dosing, and twice-monthly dosing. In other words, it is found that the administration of a bisphosphonate at a
30 high relative dosage at a low relative dosing frequency causes less adverse gastrointestinal effects, particularly esophageal effects, compared to the administration of a low relative dosage at a high relative dosing frequency. This result is surprising in view of the teachings suggesting that adverse gastrointestinal effects would be expected to
35 increase as a function of increasing bisphosphonate dosage. Such

administration methods of the present invention would be especially beneficial in treating patients that have been identified as suffering from or are susceptible to upper gastrointestinal disorders, e.g. gastrointestinal reflux disease (i.e. "GERD"), esophagitis, dyspepsia (i.e. heartburn), ulcers, and other related disorders. In such patients conventional bisphosphonate therapy could potentially exacerbate or induce such upper gastrointestinal disorders.

From a patient lifestyle standpoint, the methods of the present invention would also be more convenient than daily or cyclic dosing regimens. Patients would be subjected less frequently to the inconvenience of having to take the drug on an empty stomach and having to fast for at least 30 minutes after dosing. Also, patients would not need to keep track of a complex dosing regimen. The methods of the present invention are likely to have the advantage of promoting better patient compliance, which in turn can translate into better therapeutic efficacy.

It is an object of the present invention to provide methods for inhibiting bone resorption and the conditions associated therewith.

It is another object of the present invention to provide methods for treating abnormal bone resorption and the conditions associated therewith

It is another object of the present invention to provide methods for preventing abnormal bone resorption and the conditions associated therewith.

It is another object of the present invention to provide methods which are oral methods.

It is another object of the present invention to provide such methods in humans.

It is another object of the present invention to provide such methods in patients that have been identified as suffering from or are susceptible to upper gastrointestinal disorders, e.g. gastrointestinal reflux disease (i.e. "GERD"), esophagitis, dyspepsia (i.e. heartburn), ulcers, and other related disorders.

It is another object of the present invention to provide such methods while minimizing the occurrence of or potential for adverse gastrointestinal effects.

5 It is another object of the present invention to provide such methods comprising a continuous dosing schedule having a dosing interval selected from the group consisting of weekly dosing, twice-weekly dosing, biweekly dosing, and twice-monthly dosing.

10 It is another object of the present invention to provide such methods comprising a continuous dosing schedule having a dosing periodicity ranging from about once every 3 days to about once every 16 days.

It is another object of the present invention to provide such methods wherein the continuous dosing schedule is maintained until the desired therapeutic effect is achieved.

15 It is another object of the present invention to treat or prevent abnormal bone resorption in an osteoporotic mammal, preferably an osteoporotic human.

It is another object of the present invention to provide pharmaceutical compositions and kits useful in the methods herein.

20 These and other objects will become readily apparent from the detailed description which follows.

SUMMARY OF THE INVENTION

25 The present invention relates to methods for inhibiting bone resorption in a mammal in need thereof, while minimizing the occurrence of or potential for adverse gastrointestinal effects, said method comprising orally administering to said mammal a pharmaceutically effective amount of a bisphosphonate as a unit dosage according to a continuous schedule having a dosing interval selected
30 from the group consisting of once-weekly dosing, twice-weekly dosing, biweekly dosing, and twice-monthly dosing, wherein said continuous schedule is maintained until the desired therapeutic effect is achieved for said mammal.

35 In other embodiments, the present invention relates to methods comprising a continuous dosing schedule having a dosing

periodicity ranging from about once every 3 days to about once every 16 days.

5 In other embodiments, the present invention relates to methods for treating abnormal bone resorption in a mammal in need of such treatment.

In other embodiments, the present invention relates to methods for preventing abnormal bone resorption in a mammal in need of such prevention.

10 In other embodiments, the present invention relates to such methods useful in humans.

In other embodiments, the present invention relates to such methods useful in humans identified as having or being susceptible to upper gastrointestinal disorders.

15 In other embodiments, the present invention relates to methods for treating or preventing osteoporosis in a mammal.

In other embodiments, the present invention relates to methods for treating or preventing osteoporosis in a human.

20 In other embodiments, the present invention relates to methods for inhibiting bone resorption, or treating or preventing abnormal bone resorption in a human comprising administering to said human from about 8.75 mg to about 140 mg, on an alendronic acid active basis, of a bisphosphonate selected from the group consisting of alendronate, pharmaceutically acceptable salts thereof, and mixtures thereof.

25 In other embodiments the present invention relates to a pharmaceutical composition comprising from about 8.75 mg to about 140 mg, on an alendronic acid active basis, of a bisphosphonate selected from the group consisting of alendronate, pharmaceutically acceptable salts thereof, and mixtures thereof.

30 In other embodiments the present invention relates to a method for treating a condition or disease state in a mammal in need thereof selected from the group consisting of Paget's disease, abnormally increased bone turnover, periodontal disease, tooth loss, bone fractures, metastatic bone disease, hypercalcemia of malignancy, and multiple
35 myeloma, said method comprising orally administering to said

mammal a pharmaceutically effective amount of a bisphosphonate as a unit dosage according to a continuous schedule having a dosing interval selected from the group consisting of once-weekly dosing, twice-weekly dosing, biweekly dosing, and twice-monthly dosing.

5 In other embodiments the present invention relates to a method for preventing a condition or disease state in a mammal in need thereof selected from the group consisting of Paget's disease, abnormally increased bone turnover, periodontal disease, tooth loss, bone fractures, metastatic bone disease, hypercalcemia of malignancy, and multiple
10 myeloma, said method comprising orally administering to said mammal a pharmaceutically effective amount of a bisphosphonate as a unit dosage according to a continuous schedule having a dosing interval selected from the group consisting of once-weekly dosing, twice-weekly dosing, biweekly dosing, and twice-monthly dosing.

15 All percentages and ratios used herein, unless otherwise indicated, are by weight. The invention hereof can comprise, consist of, or consist essentially of the essential as well as optional ingredients, components, and methods described herein.

20 BRIEF DESCRIPTION OF THE FIGURES

FIG. 1 is a photomicrograph (total magnification 270X) of canine esophagus tissue (paraffin embedded and stained with hematoxylin and eosin) from an animal sacrificed immediately after infusion of the last of five separate dosages of 50 mL of simulated gastric juice administered
25 on five consecutive days.

FIG. 2 is a photomicrograph (total magnification 270X) of canine esophagus tissue (paraffin embedded and stained with hematoxylin and eosin) from an animal sacrificed immediately after infusion of the last of five separate dosages of 50 mL of 0.20 mg/mL alendronate in simulated
30 gastric juice administered on five consecutive days.

FIG. 3 is a photomicrograph (total magnification 270X) of canine esophagus tissue (paraffin embedded and stained with hematoxylin and eosin) from an animal sacrificed 24 hours after infusion with a single dosage of 50 mL of 0.80 mg/mL alendronate in simulated gastric juice.

FIG. 4 is a photomicrograph (total magnification 270X) of canine esophagus tissue (paraffin embedded and stained with hematoxylin and eosin) from an animal sacrificed 7 days after infusion with a single dosage of 50 mL of 0.80 mg/mL alendronate in simulated gastric juice.

5 FIG. 5 is a photomicrograph (total magnification 270X) of canine esophagus tissue (paraffin embedded and stained with hematoxylin and eosin) from an animal sacrificed 7 days after infusion of the last of 4 separate dosages of 50 mL of 0.80 mg/mL alendronate in simulated gastric juice administered once per week, i.e. once every 7 days.

10 FIG. 6 is a photomicrograph (total magnification 270X) of canine esophagus tissue (paraffin embedded and stained with hematoxylin and eosin) from an animal sacrificed 4 days after infusion of the last of 8 separate dosages of 50 mL of 0.40 mg/mL alendronate in simulated gastric juice administered twice per week, i.e. once every 3-4 days.

15 FIG. 7 is a photomicrograph (total magnification 270X) of canine esophagus tissue (paraffin embedded and stained with hematoxylin and eosin) from an animal sacrificed immediately after infusion of the last of five separate dosages of 50 mL of 0.20 mg/mL risedronate in simulated gastric juice administered on five consecutive days.

20 FIG. 8 is a photomicrograph (total magnification 270X) of canine esophagus tissue (paraffin embedded and stained with hematoxylin and eosin) from an animal sacrificed immediately after infusion of the last of five separate dosages of 50 mL of 4.0 mg/mL tiludronate in simulated gastric juice administered on five consecutive days.

25

DESCRIPTION OF THE INVENTION

 The present invention relates to a method, preferably an oral method, for inhibiting bone resorption in a mammal in need thereof, while minimizing the occurrence of or potential for adverse gastrointestinal effects. The present invention relates to methods of
30 treating or preventing abnormal bone resorption in a mammal in need of such treatment or prevention. The methods of the present invention comprise orally administering to a mammal a pharmaceutically effective amount of a bisphosphonate as a unit dosage, wherein said
35 dosage is administered according to a continuous schedule having a

dosing interval selected from the group consisting of once-weekly dosing, twice-weekly dosing, biweekly dosing, and twice-monthly dosing. In other embodiments, the present invention relates to methods comprising a continuous dosing schedule having a dosing periodicity ranging from
5 about once every 3 days to about once every 16 days. Typically, the continuous dosing schedule is maintained until the desired therapeutic effect is achieved for the mammal.

The present invention utilizes higher unit dosages of the bisphosphonate at each dosing point than has heretofore been typically
10 administered, yet because of the dosing schedule chosen, the potential for adverse gastrointestinal effects are minimized. Moreover, the method is more convenient because the disadvantages associated with daily dosing are minimized.

The methods of the present invention are generally
15 administered to mammals in need of bisphosphonate therapy. Preferably the mammals are human patients, particularly human patients in need of inhibiting bone resorption, such as patients in need of treating or preventing abnormal bone resorption.

The administration methods of the present invention are
20 especially useful in administering bisphosphonate therapy to human patients that have been identified as suffering from or are susceptible to upper gastrointestinal disorders, e.g. GERD, esophagitis, dyspepsia, ulcers, etc. In such patients conventional bisphosphonate therapy could potentially exacerbate or induce such upper gastrointestinal disorders.

The term "pharmaceutically effective amount", as used
25 herein, means that amount of the bisphosphonate compound, that will elicit the desired therapeutic effect or response when administered in accordance with the desired treatment regimen. A preferred pharmaceutically effective amount of the bisphosphonate is a bone
30 resorption inhibiting amount.

The term "minimize the occurrence of or potential for
adverse gastrointestinal effects", as used herein, means reducing,
preventing, decreasing, or lessening the occurrence of or the potential
for incurring unwanted side effects in the gastrointestinal tract, i.e. the
35 esophagus, stomach, intestines, and rectum, particularly the upper

gastrointestinal tract, i.e. the esophagus and stomach. Nonlimiting adverse gastrointestinal effects include, but are not limited to GERD, esophagitis, dyspepsia, ulcers, esophageal irritation, esophageal perforation, abdominal pain, and constipation.

5 The term "abnormal bone resorption", as used herein means a degree of bone resorption that exceeds the degree of bone formation, either locally, or in the skeleton as a whole. Alternatively, "abnormal bone resorption" can be associated with the formation of bone having an abnormal structure.

10 The term "bone resorption inhibiting", as used herein, means treating or preventing bone resorption by the direct or indirect alteration of osteoclast formation or activity. Inhibition of bone resorption refers to treatment or prevention of bone loss, especially the inhibition of removal of existing bone either from the mineral phase
15 and/or the organic matrix phase, through direct or indirect alteration of osteoclast formation or activity.

 The terms "continuous schedule" or "continuous dosing schedule", as used herein, mean that the dosing regimen is repeated until the desired therapeutic effect is achieved. The continuous schedule
20 or continuous dosing schedule is distinguished from cyclical or intermittent administration.

 The term "until the desired therapeutic effect is achieved", as used herein, means that the bisphosphonate compound is continuously administered, according to the dosing schedule chosen, up
25 to the time that the clinical or medical effect sought for the disease or condition is observed by the clinician or researcher. For methods of treatment of the present invention, the bisphosphonate compound is continuously administered until the desired change in bone mass or structure is observed. In such instances, achieving an increase in bone
30 mass or a replacement of abnormal bone structure with more normal bone structure are the desired objectives. For methods of prevention of the present invention, the bisphosphonate compound is continuously administered for as long as necessary to prevent the undesired condition. In such instances, maintenance of bone mass density is often
35 the objective. Nonlimiting examples of administration periods can

range from about 2 weeks to the remaining lifespan of the mammal. For humans, administration periods can range from about 2 weeks to the remaining lifespan of the human, preferably from about 2 weeks to about 20 years, more preferably from about 1 month to about 20 years, more preferably from about 6 months to about 10 years, and most preferably from about 1 year to about 10 years.

Methods of the Present Invention

The present invention comprises methods for inhibiting bone resorption in mammals. The present invention also comprises treating abnormal bone resorption in mammals. The present invention also comprises methods for preventing abnormal bone resorption in mammals. In preferred embodiments of the present invention, the mammal is a human.

The methods of the present invention do not have the disadvantages of current methods of treatment which can cause or increase the potential for adverse gastrointestinal effects or which require cumbersome, irregular, or complicated dosing regimens.

The present invention comprises a continuous dosing schedule whereby a unit dosage of the bisphosphonate is regularly administered according to a dosing interval selected from the group consisting of once-weekly dosing, twice-weekly dosing, biweekly dosing, and twice-monthly dosing.

By once-weekly dosing is meant that a unit dosage of the bisphosphonate is administered once a week, i.e. one time during a seven day period, preferably on the same day of each week. In the once-weekly dosing regimen, the unit dosage is generally administered about every seven days. A nonlimiting example of a once-weekly dosing regimen would entail the administration of a unit dosage of the bisphosphonate every Sunday. It is preferred that the unit dosage is not administered on consecutive days, but the once-weekly dosing regimen can include a dosing regimen in which unit dosages are administered on two consecutive days falling within two different weekly periods.

By twice-weekly dosing is meant that a unit dosage of the bisphosphonate is administered twice a week, i.e. two times during a

seven day period, preferably on the same two days of each weekly period. In the twice-weekly dosing regimen, each unit dosage is generally administered about every three to four days. A nonlimiting example of a twice-weekly dosing regimen would entail the administration of a unit dosage of the bisphosphonate every Sunday and Wednesday. It is preferred that the unit dosages are not administered on the same or consecutive days, but the twice-weekly dosing regimen can include a dosing regimen in which unit dosages are administered on two consecutive days within a weekly period or different weekly periods.

By biweekly dosing is meant that a unit dosage of the bisphosphonate is administered once during a two week period, i.e. one time during a fourteen day period, preferably on the same day during each two week period. In the twice-weekly dosing regimen, each unit dosage is generally administered about every fourteen days. A nonlimiting example of a biweekly dosing regimen would entail the administration of a unit dosage of the bisphosphonate every other Sunday. It is preferred that the unit dosage is not administered on consecutive days, but the biweekly dosing regimen can include a dosing regimen in which the unit dosage is administered on two consecutive days within two different biweekly periods.

By twice-monthly dosing is meant that a unit dosage of the bisphosphonate is administered twice, i.e. two times, during a monthly calendar period. With the twice-monthly regimen, the doses are preferably given on the same two dates of each month. In the twice-monthly dosing regimen, each unit dosage is generally administered about every fourteen to sixteen days. A nonlimiting example of a biweekly dosing regimen would entail dosing on or about the first of the month and on or about the fifteenth, i.e. the midway point, of the month. It is preferred that the unit dosages are not administered on the same or consecutive days but the twice-monthly dosing regimen can include a dosing regimen in which the unit dosages are administered on two consecutive days within a monthly period, or different monthly periods. The twice-monthly regimen is defined herein as being distinct from, and not encompassing, the biweekly dosing regimen because the two regimens have a different periodicity and result in the administration of

different numbers of dosages over long periods of time. For example, over a one year period, a total of about twenty four dosages would be administered according to the twice-monthly regimen (because there are twelve calendar months in a year), whereas a total of about twenty six
5 dosages would be administered according to the biweekly dosing regimen (because there are about fifty-two weeks in a year).

In further embodiments or descriptions of the present invention, the unit dosage is given with a periodicity ranging from about once every 3 days to about once every 16 days.

10 The methods and compositions of the present invention are useful for inhibiting bone resorption and for treating and preventing abnormal bone resorption and conditions associated therewith. Such conditions include both generalized and localized bone loss. Also, the creation of bone having an abnormal structure, as in Paget's disease,
15 can be associated with abnormal bone resorption.

The methods and compositions of the present invention are also useful for treating and preventing conditions such as metastatic bone disease, hypercalcemia of malignancy, multiple myeloma, periodontal disease, and tooth loss. Metastatic bone disease involves
20 tumor-induced skeletal metastases which commonly result from breast cancer, prostate cancer, lung cancer, renal cancer, thyroid cancer, and multiple myeloma. The most frequent clinical manifestations of bone metastases are pain, pathological fracture, immobility, nerve root or spinal cord compression, hypercalcemia, and compromised
25 hematopoiesis. Hypercalcemia of malignancy is also tumor-induced. It is characterized by high levels of serum calcium and is often associated with metastatic bone disease, particularly with non-ambulatory patients. Multiple myeloma is a primary tumor of the bone marrow cells. See U.S. Patent No. 5,780,455, to Brenner et al., issued July 14,
30 1998, which is incorporated by reference herein in its entirety.

The term "generalized bone loss" means bone loss at multiple skeletal sites or throughout the skeletal system. The term "localized bone loss" means bone loss at one or more specific, defined skeletal sites.

Generalized bone loss is often associated with osteoporosis. Osteoporosis is most common in post-menopausal women, wherein estrogen production has been greatly diminished. However, osteoporosis can also be steroid-induced and has been observed in males due to age.

5 Osteoporosis can be induced by disease, e.g. rheumatoid arthritis, it can be induced by secondary causes, e.g., glucocorticoid therapy, or it can come about with no identifiable cause, i.e. idiopathic osteoporosis. In the present invention, preferred methods include the treatment or prevention of abnormal bone resorption in osteoporotic humans.

10 Localized bone loss has been associated with periodontal disease, with bone fractures, and with periprosthetic osteolysis (in other words where bone resorption has occurred in proximity to a prosthetic implant).

15 Generalized or localized bone loss can occur from disuse, which is often a problem for those confined to a bed or a wheelchair, or for those who have an immobilized limb set in a cast or in traction.

The methods and compositions of the present invention are useful for treating and or preventing the following conditions or disease states: osteoporosis, which can include post-menopausal osteoporosis, steroid-induced osteoporosis, male osteoporosis, disease-induced

20 osteoporosis, idiopathic osteoporosis; Paget's disease; abnormally increased bone turnover; periodontal disease; tooth loss; localized bone loss associated with periprosthetic osteolysis; bone fractures; metastatic bone disease; hypercalcemia of malignancy; and multiple myeloma.

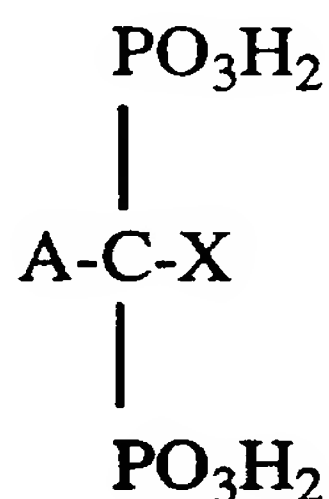
25 The methods of the present invention are intended to specifically exclude methods for the treatment and/or prevention of prosthesis loosening and prosthesis migration in mammals as described in PCT application WO 95/30421, to Goodship et al, published November 16, 1995, which is incorporated by reference herein in its

30 entirety.

Bisphosphonates

The methods and compositions of the present invention comprise a bisphosphonate. The bisphosphonates of the present

35 invention correspond to the chemical formula



wherein

5 A and X are independently selected from the group consisting of H, OH, halogen, NH₂, SH, phenyl, C1-C30 alkyl, C1-C30 substituted alkyl, C1-C10 alkyl or dialkyl substituted NH₂, C1-C10 alkoxy, C1-C10 alkyl or phenyl substituted thio, C1-C10 alkyl substituted phenyl, pyridyl, furanyl, pyrrolidinyl, imidazonyl, and benzyl.

10 In the foregoing chemical formula, the alkyl groups can be straight, branched, or cyclic, provided sufficient atoms are selected for the chemical formula. The C1-C30 substituted alkyl can include a wide variety of substituents, nonlimiting examples which include those selected from the group consisting of phenyl, pyridyl, furanyl, pyrrolidinyl, imidazonyl, NH₂, C1-C10 alkyl or dialkyl substituted NH₂, OH, SH, and C1-C10 alkoxy.

15 In the foregoing chemical formula, A can include X and X can include A such that the two moieties can form part of the same cyclic structure.

20 The foregoing chemical formula is also intended to encompass complex carbocyclic, aromatic and hetero atom structures for the A and/or X substituents, nonlimiting examples of which include naphthyl, quinolyl, isoquinolyl, adamantyl, and chlorophenylthio.

25 Preferred structures are those in which A is selected from the group consisting of H, OH, and halogen, and X is selected from the group consisting of C1-C30 alkyl, C1-C30 substituted alkyl, halogen, and C1-C10 alkyl or phenyl substituted thio.

 More preferred structures are those in which A is selected from the group consisting of H, OH, and Cl, and X is selected from the

group consisting of C1-C30 alkyl, C1-C30 substituted alkyl, Cl, and chlorophenylthio.

Most preferred is when A is OH and X is a 3-aminopropyl moiety, so that the resulting compound is a 4-amino-1,-

5 hydroxybutylidene-1,1-bisphosphonate, i.e. alendronate.

Pharmaceutically acceptable salts and derivatives of the bisphosphonates are also useful herein. Nonlimiting examples of salts include those selected from the group consisting alkali metal, alkaline metal, ammonium, and mono-, di, tri-, or tetra-C1-C30-alkyl-substituted
10 ammonium. Preferred salts are those selected from the group consisting of sodium, potassium, calcium, magnesium, and ammonium salts. Nonlimiting examples of derivatives include those selected from the group consisting of esters, hydrates, and amides.

"Pharmaceutically acceptable" as used herein means that
15 the salts and derivatives of the bisphosphonates have the same general pharmacological properties as the free acid form from which they are derived and are acceptable from a toxicity viewpoint.

It should be noted that the terms "bisphosphonate" and "bisphosphonates", as used herein in referring to the therapeutic agents
20 of the present invention are meant to also encompass diphosphonates, biphosphonic acids, and diphosphonic acids, as well as salts and derivatives of these materials. The use of a specific nomenclature in referring to the bisphosphonate or bisphosphonates is not meant to limit the scope of the present invention, unless specifically indicated. Because
25 of the mixed nomenclature currently in use by those of ordinary skill in the art, reference to a specific weight or percentage of a bisphosphonate compound in the present invention is on an acid active weight basis, unless indicated otherwise herein. For example, the phrase "about 70 mg of a bone resorption inhibiting bisphosphonate selected from the
30 group consisting of alendronate, pharmaceutically acceptable salts thereof, and mixtures thereof, on an alendronic acid active weight basis" means that the amount of the bisphosphonate compound selected is calculated based on 70 mg of alendronic acid.

Nonlimiting examples of bisphosphonates useful herein
35 include the following:

Alendronic acid, 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid.

Alendronate (also known as alendronate sodium or monosodium trihydrate), 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid monosodium trihydrate.

Alendronic acid and alendronate are described in U.S. Patents 4,922,007, to Kieczkowski et al., issued May 1, 1990, and 5,019,651, to Kieczkowski, issued May 28, 1991, both of which are incorporated by reference herein in their entirety.

Cycloheptylaminomethylene-1,1-bisphosphonic acid, YM 175, Yamanouchi (cimadronate), as described in U.S. Patent 4,970,335, to Isomura et al., issued November 13, 1990, which is incorporated by reference herein in its entirety.

1,1-dichloromethylene-1,1-diphosphonic acid (clodronic acid), and the disodium salt (clodronate, Procter and Gamble), are described in Belgium Patent 672,205 (1966) and *J. Org. Chem* 32, 4111 (1967), both of which are incorporated by reference herein in their entirety.

1-hydroxy-3-(1-pyrrolidiny)-propylidene-1,1-bisphosphonic acid (EB-1053).

1-hydroxyethane-1,1-diphosphonic acid (etidronic acid).

1-hydroxy-3-(N-methyl-N-pentylamino)propylidene-1,1-bisphosphonic acid, also known as BM-210955, Boehringer-Mannheim (ibandronate), is described in U.S. Patent No. 4,927,814, issued May 22, 1990, which is incorporated by reference herein in its entirety.

6-amino-1-hydroxyhexylidene-1,1-bisphosphonic acid (neridronate).

3-(dimethylamino)-1-hydroxypropylidene-1,1-bisphosphonic acid (olpadronate).

3-amino-1-hydroxypropylidene-1,1-bisphosphonic acid (pamidronate).

[2-(2-pyridinyl)ethylidene]-1,1-bisphosphonic acid (piridronate) is described in U.S. Patent No. 4,761,406, which is incorporated by reference in its entirety.

1-hydroxy-2-(3-pyridinyl)-ethylidene-1,1-bisphosphonic acid (risedronate).

(4-chlorophenyl)thiomethane-1,1-disphosphonic acid (tiludronate) as described in U.S. Patent 4,876,248, to Breliere et al.,
5 October 24, 1989, which is incorporated by reference herein in its entirety.

1-hydroxy-2-(1H-imidazol-1-yl)ethylidene-1,1-bisphosphonic acid (zolendronate).

Preferred are bisphosphonates selected from the group
10 consisting of alendronate, cimadronate, clodronate, tiludronate, etidronate, ibandronate, risedronate, piridronate, pamidronate, zolendronate, pharmaceutically acceptable salts thereof, and mixtures thereof.

More preferred is alendronate, pharmaceutically acceptable
15 salts thereof, and mixtures thereof.

Most preferred is alendronate monosodium trihydrate.

Pharmaceutical Compositions

Compositions useful in the present invention comprise a
20 pharmaceutically effective amount of a bisphosphonate. The bisphosphonate is typically administered in admixture with suitable pharmaceutical diluents, excipients, or carriers, collectively referred to herein as "carrier materials", suitably selected with respect to oral administration, i.e. tablets, capsules, elixirs, syrups, effervescent
25 compositions, powders, and the like, and consistent with conventional pharmaceutical practices. For example, for oral administration in the form of a tablet, capsule, or powder, the active ingredient can be combined with an oral, non-toxic, pharmaceutically acceptable inert carrier such as lactose, starch, sucrose, glucose, methyl cellulose,
30 magnesium stearate, mannitol, sorbitol, croscarmellose sodium and the like; for oral administration in liquid form, e.g., elixirs, syrups, and effervescent compositions, the oral drug components can be combined with any oral, non-toxic, pharmaceutically acceptable inert carrier such as ethanol, glycerol, water and the like. Moreover, when desired or
35 necessary, suitable binders, lubricants, disintegrating agents, buffers,

coatings, flavoring agents, and coloring agents can also be incorporated. Suitable binders can include starch, gelatin, natural sugars such as glucose, anhydrous lactose, free-flow lactose, beta-lactose, and corn sweeteners, natural and synthetic gums, such as acacia, guar,
5 tragacanth or sodium alginate, carboxymethyl cellulose, polyethylene glycol, waxes, and the like. Lubricants used in these dosage forms include sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride and the like. A particularly preferred tablet formulation for alendronate monosodium trihydrate is
10 that described in U.S. Patent No. 5,358,941, to Bechard et al, issued October 25, 1994, which is incorporated by reference herein in its entirety. The compounds used in the present method can also be coupled with soluble polymers as targetable drug carriers. Such polymers can include polyvinylpyrrolidone, pyran copolymer, polyhydroxylpropyl-
15 methacrylamide, and the like.

The precise dosage of the bisphosphate will vary with the dosing schedule, the oral potency of the particular bisphosphonate chosen, the age, size, sex and condition of the mammal or human, the nature and severity of the disorder to be treated, and other relevant
20 medical and physical factors. Thus, a precise pharmaceutically effective amount cannot be specified in advance and can be readily determined by the caregiver or clinician. Appropriate amounts can be determined by routine experimentation from animal models and human clinical studies. Generally, an appropriate amount of bisphosphonate is
25 chosen to obtain a bone resorption inhibiting effect, i.e. a bone resorption inhibiting amount of the bisphosphonate is administered. For humans, an effective oral dose of bisphosphonate is typically from about 1.5 to about 6000 $\mu\text{g/kg}$ body weight and preferably about 10 to about 2000 $\mu\text{g/kg}$ of body weight.

30 For human oral compositions comprising alendronate, pharmaceutically acceptable salts thereof, or pharmaceutically acceptable derivatives thereof, a unit dosage typically comprises from about 8.75 mg to about 140 mg of the alendronate compound, on an alendronic acid active weight basis.

For once-weekly dosing, an oral unit dosage comprises from about 17.5 mg to about 70 mg of the alendronate compound, on an alendronic acid active weight basis. Examples of weekly oral dosages include a unit dosage which is useful for osteoporosis prevention
5 comprising about 35 mg of the alendronate compound, and a unit dosage which is useful for treating osteoporosis comprising about 70 mg of the alendronate compound.

For twice-weekly dosing, an oral unit dosage comprises from about 8.75 mg to about 35 mg of the alendronate compound, on an
10 alendronic acid active weight basis. Examples of twice-weekly oral dosages include a unit dosage which is useful for osteoporosis prevention comprising about 17.5 mg of the alendronate compound, and a unit dosage which is useful for osteoporosis treatment, comprising about 35 mg of the alendronate compound.

15 For biweekly or twice-monthly dosing, an oral unit dosage comprises from about 35 mg to about 140 mg of the alendronate compound, on an alendronic acid active weight basis. Examples of biweekly or twice-monthly oral dosages include a unit dosage which is useful for osteoporosis prevention comprising about 70 mg of the
20 alendronate compound, and a unit dosage which is useful for osteoporosis treatment, comprising about 140 mg of the alendronate compound.

Nonlimiting examples of oral compositions comprising alendronate, as well as other bisphosphonates, are illustrated in the
25 Examples, below.

Sequential Administration Of Histamine H2 Receptor Blockers And/Or Proton Pump Inhibitors With Bisphosphonates

In further embodiments, the methods and compositions of
30 the present invention can also comprise a histamine H2 receptor blocker (i.e. antagonist) and/or a proton pump inhibitor. Histamine H2 receptor blockers and proton pump inhibitors are well known therapeutic agents for increasing gastric pH. See L.J. Hixson, et al., *Current Trends in the Pharmacotherapy for Peptic Ulcer Disease*, *Arch. Intern. Med.*, vol. 152,
35 pp. 726-732 (April 1992), which is incorporated by reference herein in its

entirety. It is found in the present invention that the sequential oral administration of a histamine H2 receptor blocker and/or a proton pump inhibitor, followed by a bisphosphonate can help to further minimize adverse gastrointestinal effects. In these embodiments, the histamine H2 receptor blocker and/or proton pump inhibitor is administered from about 30 minutes to about 24 hours prior to the administration of the bisphosphonate. In more preferred embodiments, the histamine H2 receptor blocker and/or proton pump inhibitor is administered from about 30 minutes to about 12 hours prior to the administration of the bisphosphonate.

The dosage of the histamine H2 receptor blocker and/or proton pump inhibitor will depend upon the particular compound selected and factors associated with the mammal to be treated, i.e. size, health, etc.

Nonlimiting examples of histamine H2 receptor blockers and/or proton pump inhibitors include those selected from the group consisting of cimetidine, famotidine, nizatidine, ranitidine, omeprazole, and lansoprazole.

Treatment Kits

In further embodiments, the present invention relates to a kit for conveniently and effectively carrying out the methods in accordance with the present invention. Such kits are especially suited for the delivery of solid oral forms such as tablets or capsules. Such a kit preferably includes a number of unit dosages. Such kits can include a card having the dosages oriented in the order of their intended use. An example of such a kit is a "blister pack". Blister packs are well known in the packaging industry and are widely used for packaging pharmaceutical unit dosage forms. If desired, a memory aid can be provided, for example in the form of numbers, letters, or other markings or with a calendar insert, designating the days in the treatment schedule in which the dosages can be administered. Alternatively, placebo dosages, or calcium or dietary supplements, either in a form similar to or distinct from the bisphosphonate dosages, can be included to provide a kit in which a dosage is taken every day. In those

embodiments including a histamine H2 receptor and/or proton pump inhibitor, these agents can be included as part of the kit.

EXAMPLES

5 The following examples further describe and demonstrate embodiments within the scope of the present invention. The examples are given solely for the purpose of illustration and are not to be construed as limitations of the present invention as many variations thereof are possible without departing from the spirit and scope of the invention.

10

EXAMPLE 1

Esophageal Irritation Potential

15 The esophageal irritation potential of the bisphosphonates is evaluated using a dog model.

 The experiments demonstrate the relative irritation potential of the following dosing regimens: placebo (Group 1), a single high concentration dosage of alendronate monosodium trihydrate (Group 2), a low concentration dosage of alendronate monosodium trihydrate administered for five consecutive days (Groups 3 and 4), a high concentration dosage of alendronate monosodium trihydrate administered once per week for four weeks (Group 5), a mid-range concentration dosage of alendronate monosodium trihydrate administered twice per week for four weeks (Group 6), a low dosage of risedronate sodium administered for five consecutive days (Group 7), and a low dosage of tiludronate disodium administered for five consecutive days (Group 8).

 The following solutions are prepared:

- 30 (1) simulated gastric juice (pH about 2), i.e. the control solution.
- (2) simulated gastric juice (pH about 2) containing about 0.20 mg/mL of alendronate monosodium trihydrate on an alendronic acid active basis.

- 5
- (3) simulated gastric juice (pH about 2) containing about 0.80 mg/mL of alendronate monosodium trihydrate on an alendronic acid active basis.
- (4) simulated gastric juice (pH about 2) containing about 0.40 mg/mL of alendronate monosodium trihydrate on an alendronic acid active basis.
- (5) simulated gastric juice (pH about 2) containing about 0.20 mg/mL of risedronate sodium on a risedronic acid active basis.
- 10 (6) simulated gastric juice (pH about 2) containing about 4.0 mg/mL of tiludronate disodium on a tiludronic acid active basis.

15 The simulated gastric juice is prepared by dissolving about 960 mg of pepsin (L-585,228000B003, Fisher Chemical) in about 147 mL of 0.90 (wt %) NaCl (aqueous), adding about 3mL of 1.0 M HCl (aqueous), and adjusting the volume to about 300 mL with deionized water. The pH of the resulting solution is measured and if necessary is adjusted to about 2 using 1.0 M HCl (aqueous) or 1.0 M NaOH (aqueous).

20 The animals used in the experiments are anesthetized and administered about 50 mL of the appropriate solution over about 30 minutes by infusion into the esophagus using an infusion pump and a rubber catheter. The following treatment experiments are run:

25 Group 1: This control group contains four animals. Each animal is administered a dosage of about 50 mL of simulated gastric juice [solution (1)] on each of five consecutive days. The animals are sacrificed immediately after the last dose is administered.

30 Group 2: This group contains four animals. Each animal is administered a dosage of about 50 mL of simulated gastric juice containing about 0.20 mg/mL of alendronate [solution (2)] on each of five consecutive days. The animals are sacrificed immediately after the last dose is administered.

35

- 5 Group 3: This group contains five animals. Each animal is administered a dosage of about 50 mL of simulated gastric juice containing about 0.80 mg/mL of alendronate [solution (3)] on a single treatment day. The animals are sacrificed about 24 hours after the dose is administered.
- 10 Group 4: This group contains five animals. Each animal is administered a dosage of about 50 mL of simulated gastric juice containing about 0.80 mg/mL of alendronate [solution (3)] on a single treatment day. The animals are sacrificed about 7 days after the dose is administered.
- 15 Group 5: This group contains six animals. Each animal is administered a dosage of about 50 mL of simulated gastric juice containing about 0.80 mg/mL of alendronate [solution (3)] once per week, i.e. every seven days, for four weeks. The animals are administered a total of four dosages. The animals are sacrificed about 7 days after the last dose is administered.
- 20 Group 6: This group contains six animals. Each animal is administered a dosage of about 50 mL of simulated gastric juice containing about 0.40 mg/mL of alendronate [solution (4)] twice per week, i.e. every three to four days, for four weeks. The animals are administered a total of eight dosages. The animals are sacrificed about four days after the last dose is administered.
- 25 Group 7: This group contains eight animals. Each animal is administered a dosage of about 50 mL of simulated gastric juice containing about 0.20 mg/mL of risedronate [solution (5)] on each of five consecutive days. The animals are sacrificed immediately after the last dose is administered.
- 30 Group 8: This group contains four animals. Each animal is administered a dosage of about 50 mL of simulated gastric juice containing about 4.0 mg/mL of tiludronate [solution (6)] on each of
- 35

five consecutive days. The animals are sacrificed immediately after the last dose is administered.

5 The esophagus from each sacrificed animal is removed and prepared for histopathology using standard techniques by embedding the tissue in paraffin, staining with hematoxylin and eosin. The sections are examined microscopically. The histopathology results are summarized in Table 1.

10 For the Group 1 animals (control group), the photomicrographs show that the esophagus is normal with an intact epithelium and absence of inflammatory cells in the submucosa. FIG. 1 is a representative photomicrograph from a Group 1 animal.

15 For the Group 2 animals, the photomicrographs show that the esophagus exhibits deep ulceration of the epithelial surface and marked submucosal inflammation and vacuolation. FIG. 2 is a representative photomicrograph from a Group 2 animal.

20 For the Group 3 animals, the photomicrographs show that the esophagus has an intact epithelial surface with very slight submucosal inflammation and vacuolation. FIG. 3 is a representative photomicrograph from a Group 3 animal.

25 For the Group 4 animals, the photomicrographs show that the esophagus has an intact epithelium with either minimal inflammation (two of the five animals) or no inflammation (three of the five animals) and no vacuolation. FIG. 4 is a representative photomicrograph from a Group 4 animal exhibiting minimal inflammation.

30 For the Group 5 animals, the photomicrographs show that the esophagus is normal with an intact epithelium and absence of inflammatory cells in the submucosa. FIG. 5 is a representative photomicrograph from a Group 5 animal.

For the Group 6 animals, the photomicrographs show that the esophagus exhibits deep ulceration of the epithelial surface and marked submucosal inflammation and vacuolation. FIG. 6 is a representative photomicrograph from a Group 6 animal.

For the Group 7 animals, the photomicrographs show that the esophagus exhibits deep ulceration of the epithelial surface and marked submucosal inflammation and vacuolation. FIG. 7 is a representative photomicrograph from a Group 7 animal.

5 For the Group 8 animals, the photomicrographs show that the esophagus exhibits slight ulceration of the epithelial surface and slight submucosal inflammation and vacuolation. FIG. 8 is a representative photomicrograph from a Group 8 animal.

10 These experiments demonstrate that considerably less esophageal irritation (comparable to control Group 1) is observed from the administration of a single high concentration dosage of alendronate (Groups 3 and 4) versus administration of low concentration dosages on consecutive days (Group 2). These experiments also demonstrate
15 considerably less esophageal irritation is observed from the administration of a single high concentration of alendronate on a weekly basis (Group 5) or twice-weekly basis (Group 6) versus administration of low concentration dosages on consecutive days (Group 2). These
20 experiments also demonstrate that when other bisphosphonates such as risedronate (Group 7) or tiludronate (Group 8) are administered at low dosages on consecutive days that the esophageal irritation potential is high.

Table 1.

Esophageal Irritation Potential Studies				
Group	Active Agent mg/mL	Dosing Schedule	Sacrifice Time	Histo-pathology
1 (n=4)	0	1X daily for 5 days	immediately after last dosing	Normal. Intact epithelium and absence of inflammatory cells in the submucosa.
2 (n=4)	Alendronate 0.20	1X daily for 5 days	immediately after last dosing	Deep ulceration of epithelial surface. Marked submucosal inflammation and vacuolation.
3 (n=5)	Alendronate 0.80	1X	24 hours after dosing	Intact epithelial surface with very slight submucosal inflammation and vacuolation.
4 (n=5)	Alendronate 0.80	1X	7 days after dosing	Intact epithelium with either minimal inflammation (2 of 5 animals) or no inflammation (3 of 5 animals) and no vacuolation.
5 (n=6)	Alendronate 0.80	1X weekly for a total of 4 doses	7 days after last dosing	Intact epithelium with no inflammation and no vacuolation.

6 (n=6)	Alendronate 0.40	2X weekly for 4 weeks	immediate ly after last dosing	Deep ulceration of epithelial surface. Marked submucosal inflammation and vacuolation.
7 (n=8)	Risedronate 0.20	1X daily for 5 days	immediate ly after last dosing	Deep ulceration of epithelial surface (4 of 8 animals). Marked submucosal inflammation and vacuolation.
8 (n=4)	Tiludronate 4.0	1X daily for 5 days	24 hours after last dosing	Slight submucosal inflammation and vacuolation (3 of 4 animals, including 1 of these animals with slight ulceration).

EXAMPLE 2

Once-weekly dosing regimen.

5

Treatment of osteoporosis.

Alendronate tablets or liquid formulations containing about 70 mg of alendronate, on an alendronic acid active basis, are prepared (see EXAMPLES 7 and 8). The tablets or liquid formulations are orally administered to a human patient once-weekly, i.e. preferably about once every seven days (for example, every Sunday), for a period of at least one year. This method of administration is useful and convenient for treating osteoporosis and for minimizing adverse gastrointestinal effects, particularly adverse esophageal effects. This method is also useful for improving patient acceptance and compliance.

15

Prevention of osteoporosis.

Alendronate tablets or liquid formulations containing about 35 mg of alendronate, on an alendronic acid active basis, are prepared (see EXAMPLES 7 and 8). The tablets or liquid formulations are orally administered to a human patient once-weekly, i.e. preferably about once every seven days (for example, every Sunday), for a period of at least one year. This method of administration is useful and convenient for preventing osteoporosis and for minimizing adverse gastrointestinal effects, particularly adverse esophageal effects. This method is also useful for improving patient acceptance and compliance.

EXAMPLE 3

Twice-weekly dosing regimen.

Treatment of osteoporosis.

Alendronate tablets or liquid formulations containing about 35 mg of alendronate, on an alendronic acid active basis, are prepared (see EXAMPLES 7 and 8). The tablets or liquid formulations are orally administered to a human patient twice-weekly, preferably about once every three or four days (for example, every Sunday and Wednesday), for a period of at least one year. This method of administration is useful and convenient for treating osteoporosis and for minimizing adverse gastrointestinal effects, particularly adverse esophageal effects. This method is also useful for improving patient acceptance and compliance.

Prevention of osteoporosis.

Alendronate tablets or liquid formulations containing about 17.5 mg of alendronate, on an alendronic acid active basis, are prepared (see EXAMPLES 7 and 8). The tablets or liquid formulations are orally administered to a human patient twice-weekly, preferably about once every three or four days (for example, every Sunday and Wednesday), for a period of at least one year. This method of administration is useful and convenient for preventing osteoporosis and for minimizing adverse

gastrointestinal effects, particularly adverse esophageal effects. This method is also useful for improving patient acceptance and compliance.

EXAMPLE 4

5

Biweekly dosing regimen

Treatment of osteoporosis.

10 Alendronate tablets or liquid formulations containing about
140 mg of alendronate, on an alendronic acid active basis, are prepared
(see EXAMPLES 7 and 8). The tablets or liquid formulations are orally
administered to a human patient biweekly, i.e. preferably about once
every fourteen days (for example, on alternate Sundays), for a period of
at least one year. This method of administration is useful and
15 convenient for treating osteoporosis and for minimizing adverse
gastrointestinal effects, particularly adverse esophageal effects. This
method is also useful for improving patient acceptance and compliance.

Prevention of osteoporosis.

20 Alendronate tablets or liquid formulations containing about
70 mg of alendronate, on an alendronic acid active basis, are prepared
(see EXAMPLES 7 and 8). The tablets or liquid formulations are orally
administered to a human patient biweekly, i.e. preferably about once
every fourteen days (for example, on alternate Sundays), for a period of
25 at least one year. This method of administration is useful and
convenient for preventing osteoporosis and for minimizing adverse
gastrointestinal effects, particularly adverse esophageal effects. This
method is also useful for improving patient acceptance and compliance.

30

EXAMPLE 5

Twice-monthly dosing regimen.

Treatment of osteoporosis.

Alendronate tablets or liquid formulations containing about 140 mg of alendronate, on an alendronic acid active basis, are prepared (see EXAMPLES 7 and 8). The tablets or liquid formulations are orally administered to a human twice-monthly, i.e. preferably about once every fourteen to sixteen days (for example, on about the first and fifteenth of each month), for a period of at least one year. This method of administration is useful and convenient for treating osteoporosis and for minimizing adverse gastrointestinal effects, particularly adverse esophageal effects. This method is also useful for improving patient acceptance and compliance.

Prevention of osteoporosis.

Alendronate tablets or liquid formulations containing about 70 mg of alendronate, on an alendronic acid active basis, are prepared (see EXAMPLES 7 and 8). The tablets or liquid formulations are orally administered to a human patient biweekly, i.e. preferably once every fourteen to sixteen days (for example, on about the first and fifteenth of each month), for a period of at least one year. This method of administration is useful and convenient for preventing osteoporosis and for minimizing adverse gastrointestinal effects, particularly adverse esophageal effects. This method is also useful for improving patient acceptance and compliance.

EXAMPLE 6

In further embodiments, alendronate tablets or liquid formulations are orally dosed, at the desired dosage, according to the dosing schedules of EXAMPLES 2-5, for treating or preventing other disorders associated with abnormal bone resorption.

In yet further embodiments, other bisphosphonate compounds are orally dosed, at the desired dosage, according to the dosing schedules of EXAMPLES 2-5, for treating or preventing osteoporosis or for treating or preventing other conditions associated with abnormal bone resorption.

EXAMPLE 7

Bisphosphonate tablets.

5 Bisphosphonate containing tablets are prepared using standard mixing and formation techniques as described in U.S. Patent No. 5,358,941, to Bechard et al., issued October 25, 1994, which is incorporated by reference herein in its entirety.

10 Tablets containing about 35 mg of alendronate, on an alendronic acid active basis, are prepared using the following relative weights of ingredients.

	<u>Ingredient</u>	<u>Per Tablet</u>	<u>Per 4000 Tablets</u>
15	Alendronate Monosodium Trihydrate	45.68 mg	182.72 g
	Anhydrous Lactose, NF	71.32 mg	285.28 g
	Microcrystalline Cellulose, NF	80.0 mg	320.0 g
20	Magnesium Stearate, NF	1.0 mg	4.0 g
	Croscarmellose Sodium, NF	2.0 mg	8.0 g

25 The resulting tablets are useful for administration in accordance with the methods of the present invention for inhibiting bone resorption.

30 Similarly, tablets comprising other relative weights of alendronate, on an alendronic acid active basis are prepared: e.g., about 8.75, 17.5, 70, and 140 mg per tablet. Also, tablets containing other bisphosphonates at appropriate active levels are similarly prepared: e.g., cimadronate, clodronate, tiludronate, etidronate, ibandronate, risedronate, piridronate, pamidronate, zolendronate, and pharmaceutically acceptable salts thereof. Also, tablets containing
35 combinations of bisphosphonates are similarly prepared.

EXAMPLE 8

Liquid Bisphosphonate Formulation.

5

Liquid bisphosphonate formulations are prepared using standard mixing techniques.

10 A liquid formulation containing about 70 mg of alendronate monosodium trihydrate, on an alendronic acid active basis, per about 75 mL of liquid is prepared using the following relative weights of ingredients.

	<u>Ingredient</u>	<u>Weight</u>
15	Alendronate Monosodium Trihydrate	91.35 mg
	Sodium Propylparaben	22.5 mg
	Sodium Butylparaben	7.5 mg
	Sodium Citrate Dihydrate	1500 mg
20	Citric Acid Anhydrous	56.25 mg
	Sodium Saccharin	7.5 mg
	Water	qs 75 mL
	1 N Sodium Hydroxide (aq)	qs pH 6.75

25 The resulting liquid formulation is useful for administration as a unit dosage in accordance with the methods of the present invention for inhibiting bone resorption.

30 Similarly, liquid formulations comprising other relative weights of alendronate, on an alendronic acid active basis, per unit dosage are prepared: e.g., about 8.75, 17.5, 35, and 140 mg per 75 mL volume. Also, the liquid formulations are prepared to provide other volumes for the unit dosage, e.g. about 135 mL. Also, the liquid formulations are prepared containing other bisphosphonates at appropriate active levels: e.g., **cimadronate**, clodronate, tiludronate, 35 etidronate, ibandronate, risedronate, **piridronate**, pamidronate,

zolendronate, and pharmaceutically acceptable salts thereof. Also, liquid formulations containing combinations of bisphosphonates are similarly prepared.

WHAT IS CLAIMED IS:

1. A method for treating a condition or disease state in a mammal in need thereof selected from the group consisting of Paget's
5 disease, abnormally increased bone turnover, periodontal disease, tooth loss, bone fractures, metastatic bone disease, hypercalcemia of malignancy, and multiple myeloma, said method comprising orally administering to said mammal a pharmaceutically effective amount of a bisphosphonate as a unit dosage according to a continuous schedule
10 having a dosing interval selected from the group consisting of once-weekly dosing, twice-weekly dosing, biweekly dosing, and twice-monthly dosing.
2. A method according to Claim 1 wherein said mammal is
15 a human.
3. A method according to Claim 2 wherein said bisphosphonate is selected from the group consisting of alendronate, cimidronate, clodronate, tiludronate, etidronate, ibandronate,
20 risedronate, piridronate, pamidronate, zolendronate, pharmaceutically acceptable salts thereof, and mixtures thereof.
4. A method according to claim 3 wherein said bisphosphonate is alendronate, pharmaceutically acceptable salts
25 thereof, and mixtures thereof.
5. A method according to claim 4 wherein said bisphosphonate is alendronate monosodium trihydrate.
6. A method for preventing a condition or disease state in a
30 mammal in need thereof selected from the group consisting of Paget's disease, abnormally increased bone turnover, periodontal disease, tooth loss, bone fractures, metastatic bone disease, hypercalcemia of malignancy, and multiple myeloma, said method comprising orally
35 administering to said mammal a pharmaceutically effective amount of a

bisphosphonate as a unit dosage according to a continuous schedule having a dosing interval selected from the group consisting of once-weekly dosing, twice-weekly dosing, biweekly dosing, and twice-monthly dosing.

5

7. A method according to Claim 6 wherein said mammal is a human.

8. A method according to Claim 7 wherein said
10 bisphosphonate is selected from the group consisting of alendronate, cimidronate, clodronate, tiludronate, etidronate, ibandronate, risedronate, piridronate, pamidronate, zolendronate, pharmaceutically acceptable salts thereof, and mixtures thereof.

15 9. A method according to claim 8 wherein said bisphosphonate is alendronate, pharmaceutically acceptable salts thereof, and mixtures thereof.

10 20 10. A method according to claim 9 wherein said bisphosphonate is alendronate monosodium trihydrate.



Application No: GB 9819243.8
Claims searched: 1-10

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Databases searched:

UK Patent Office collections, including GB, EP, WO & US patent specifications, in:

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Other: On-line: CAS-ONLINE, MEDLINE, ADISINSIGHT, PHAR, OPTICS

Documents considered to be relevant:

Category	Identity of document and relevant passage	Relevant to claims
X	WO 95/30421 A1 (CIBA GEIGY AG) whole document particularly p 7, ll 6-18, examples 1 & 5	1-10
A	WO 95/28145 A1 (PROCTER & GAMBLE) p 1, ll 24-30, p 5, ll 33-40, p 6, l 4 - p 7, l 2, p 9, ll 21-24, p 13, ll 5-8, examples I and II.	1-10
X	EP 0 600 834 A1 (CIBA GEIGY AG) whole document particularly p 7, l 39 - p 8, l 19, examples 1 & 4.	1-10
X	US 5 488 041 (BARBIER et al.) whole document particularly col. 1, l 54 - col. 2, l 27, col. 3, ll 10-36.	1-10
X	US 4 980 171 (FELS et al.) col. 2, l 5 - col. 3, l 5, col. 3, ll 18-28, 41-45, col. 4, l 50 - col. 6, l 57.	1-10

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